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LETTERS AND CORRESPONDENCE

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β-Thalassemia Trait Might Increase the Severity of Hemochromatosis in Subjects With the C282Y Mutation in the HFE Gene

To the Editor: The association between hereditary hemochromatosis and thalassemia syndrome might lead to a severe iron overload [1,2], but the results are still controversial. By PCR and restriction enzyme digestion [3], we analyzed the C282Y and H63D mutations in the HFE gene in one family whose propositus carried the β-thalassemia trait. The patient was a female, 38 years old, presenting weakness and arthralgia. She had 4 children and received transfusion (1 unit of red cell) during her last gestation. She did not present diabetes or cardiac disease and her hepatic enzymes were normal. Her mother and 2 sons also carried the β-thalassemia trait.

TABLE I

	Propositus	Son 1	Son 2	Mother	Father
Age (years)	38	12	8	61	72
Hb (g/dL)	11.9	11.3	10.8	10.9	16.7
RBC ($\times 10^{12}$/L)	5.50	5.97	5.66	5.26	5.27
MCV (fL)	67	61	60	65	89
MCH (pg)	21.6	19	19.1	20.8	31.6
RDW (%)	15.7	16.1	16.3	16.8	13.6
% HbA_2[a]	5.3	6.0	5.4	4.6	2.3
Transferrin saturation (%)	88	36	29	42	35
Ferritin (μg/L)[b]	2,162	144	56	382	185
C282Y	+/+	+/+	+/−	+/−	+/−
H63D	−/−	−/−	+/−	−/−	−/−

[a]Quantitation of A2 hemoglobin was carried out by elution (Weatherall and Clegg, 1981) and normal values are 1.5 to 3.4%.
[b]Normal values (10–300 μg/L, kit Baxter).

The propositus and one 8-year-old son were homozygous for the C282Y mutation, while her mother and the other son were heterozygous for the C282Y mutation. The H63D was absent in all family members except in this last child, a 4-year-old boy who presented both mutations in the heterozygous form.

In the family studied here, we observed that the propositus, who was homozygous for the C282Y mutation and heterozygous for β-thalassemia, also presented a very high serum ferritin level, uncommon for patients at this age [4]. Corroborating this data, Piperno et al. observed a more severe phenotype expression of hemochromatosis in two β-thalassemic patients, homozygous for the C282Y mutation. This author also discussed the possibility that a single HFE gene mutation and the co-existence of β-thalassemia trait might produce a relatively mild hemochromatosis-like phenotype. Our results support this hypothesis because, in the family here reported, the mother, who carried the β-thalassemia trait and was heterozygous for the C282Y mutation, presented a level of ferritin and transferrin saturation slightly above the normal. On the other hand, the father, who does not present the β-thalassemia trait but is heterozygous for the C282Y mutation, did not have abnormal levels of ferritin or transferrin saturation (Table I). Taken together, these results suggest that mutations in the HFE gene associated with β-thalassemia trait might lead to an excessive iron absorption and increased severity of hemochromatosis.

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Successful Autologous Stem Cell Transplantation in Aggressive Prolymphocytic Leukemia

To the Editor: B-prolymphocytic leukemia (PLL) is an aggressive lymphoid disorder with a short survival. Although there have been reports on response to splenectomy, splenic irradiation, and chemotherapy, optimal treatment remains unclear [1]. We have recently treated a patient with aggressive PLL with high-doses chemotherapy and autologous peripheral blood stem cell transplantation (PBSCT).

A 57-year-old patient presented with leukocytosis found on routine examination on July 1996. Physical examination revealed spleen palpated 4 cm below the left costal margin. No peripheral lymph nodes were palpated. The complete blood count (CBC) revealed Hb 13.9 g/dL, WBC 38.1 × 10^9/L (84% prolymphocytes), and Plt 112 × 10^9/L. The serum IgG was 414 mg/dL (normal 1,020–1,460). A minimal monoclonal IgG λ peak was found by immunoelectrophoresis and immunofixation. β2-microglobulin was 3,130 μg/L (normal up to 2,500). The circulating prolymphocytes expressed HLA-DR, CD19, CD5, CD38, PCA1, FMC7, and surface IgG. Abdominal ultrasound showed an enlarged spleen 19 cm. Bone marrow (BM) biopsy showed diffuse infiltrate by small lymphocytes and prolymphocytes. A FISH analysis revealed a deletion of chromosome 13q14, while no trisomy 12 or p53 deletion was evident. The diagnosis of B-PLL was established. A constant increase in the size of the spleen and the number of circulating prolymphocytes (above 50 × 10^9/L) during follow-up led us to initiate treatment. Six monthly courses of chlorambucil and prednisone elicited no response. Splenic irradiation (340 cGy) followed by a 5-day course of 2CDA (0.1 mg/kg/day) resulted in normalization of the spleen size and CBC. We recommended this approach for PLL previously [2]. Ten months later the patient presented with a massive splenomegaly, leukocytosis 20.2 × 10^9/L (76% prolymphocytes) and a packed BM. Only a short remission was achieved with a second 2CDA treatment. We decided to have a more aggressive approach consisting of high-dose chemotherapy followed by autologous PBSCT. We used a combination of 25 mg/m^2 fludarabine for 3 days, 8 mg/m^2 mitoxantrone for 1 day, and 200 mg/m^2 cyclophosphamide for 3 days [3]. After three cycles, the WBC count was 3.3 × 10^9/L, while 15% of the circulating mononuclear cells were CD5/CD19$^+$. Subsequently we performed a mobilization of PBSC by cyclophosphamide 1.5 g/m^2 and G-CSF (filgrastim, 10 μg/kg). With 4 leukapheresis procedures (Haemonetics, MCS$^+$), 11.5 × 10^6/kg CD34$^+$ and 0.6 × 10^6/kg CD5/CD19$^+$ cells were harvested. On January 1999 we treated the patient according to the myeloablative CBV protocol (30 mg/kg cyclophosphamide for 4 days, 200 mg/m^2 BCNU for 2 days, and 300 mg/m^2 VP-16 for 4 days) followed by reinfusion of the unmanipulated autograft.

Hematological recovery was rapid (>0.5 × 10^9 WBC on day 11), complications were limited to transient neutropenic fever and mucositis. Eight months after PBSCT the patient is well, the spleen is not palpable, WBC 9.2 × 10^9/L (16% lymphocytes), circulating CD5/CD19$^+$ cells 7%, β2 microglobulin 2200 μg/L, IgG 673 mg/dL, and paraprotein is not detected. Bone marrow biopsy reveals minimal focal lymphocytosis.

High-dose chemotherapy and PBSCT were very effective in this aggressive PLL case. Recently published reports suggest that myeloablative treatment with subsequent autologous PBSCT may have curative potential in high-risk CLL [4]. Only few PLL cases treated by transplant have been reported, to our knowledge the PLL patients underwent allogeneic transplantation [5].

In conclusion, our high-risk PLL patient, previously treated with fludarabine, demonstrated successful recruitment and engraftment of autologous PBSC. We used an unmanipulated PB harvest. Major efforts are made in CLL and lymphoma for achievement an autograft free from tumor cells. Further chemotherapy given to eliminate residual tumor cells may result in cumulative marrow toxicity with a low yield in cell collections, a high risk of autoimmune disorders, and infections. Harvested PBSC even in the presence of residual leukemic cells is sufficient to restore a normal polyclonal hematopoiesis after the autografting. We believe that stem cell collection is recommended in PLL as soon as the first optimal response is achieved despite evidence of residual disease.

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Diffuse Large-Cell B-Cell Lymphoma in a Pituitary Adenoma: An Unusual Cause of Pituitary Apoplexy

To the Editor: Pituitary apoplexy is an uncommon endocrine and neurosurgical emergency, usually caused by rapid enlargement of a pituitary adenoma. Acute anterior hypopituitarism caused by lymphoma has rarely been reported. We describe a case of acute pituitary failure in which the tumor tissue from the pituitary gland showed a pituitary adenoma and a diffuse large-cell B-cell lymphoma.

An 82-year-old Chinese man presented with headache and rapidly deteriorating vision. Physical examination showed right side blindness, left temporal hemianopia, and bilateral papilloedema. Serum biochemistry and endocrine investigations confirmed pan-hypopituitarism (126 mmol/L sodium, 3.7 mmol/L potassium, 2.3 mmol/L glucose, 11 (normal 12–23) pmol/L free thyroxine, 0.77 (normal 0.35–5.5) mIU/L thyroid-stimulating hormone, 29 (normal 150–720) nmol/L morning cortisol, 21 (normal 9–52) pg/mL adrenocorticotrophic hormone, 399 (normal <500) mIU/L prolactin). Magnetic resonance imaging (MRI) of the brain showed a heterogeneously isointense bilobed tumor enlarging the pituitary fossa (Fig. 1A). The hypothalamus and optic chiasma were severely compressed. A transphenoidal biopsy showed a collision tumor consisting of a viable pituitary adenoma and a malignant lymphoma. The adenoma was formed by diffuse sheets of cuboidal endocrine cells in a vascular stroma, which showed immunoreactivity to chromogranin and synaptophysin, and weak TSH positivity. The cells did not stain for follicle stimulating hormone, growth hormone, or prolactin. The lymphoma was closely admixed with the adenoma, and consisted of diffuse large lymphoma cells, with CD20 (Dako, Glostrup, Denmark) expression (Fig. 1B). Serological test for human immunodeficiency virus (HIV) was negative. The patient and his family only opted for palliative involved field radiotherapy.

Pituitary apoplexy is an uncommon clinical syndrome and is usually a result of hemorrhage or infarction of a pituitary adenoma. Metastatic tumors as a cause of pituitary apoplexy are very rare. Most metastatic tumors affect the posterior lobe [1], leading to diabetes insipidus. Anterior hypopituitarism is rarely a manifestation of metastasis, as a large portion of the anterior pituitary gland has to be destroyed before the tumor is clinically evident; and patients rarely live long enough. Consistent with this pattern of infiltration, the few reported cases of lymphoma involving the pituitary

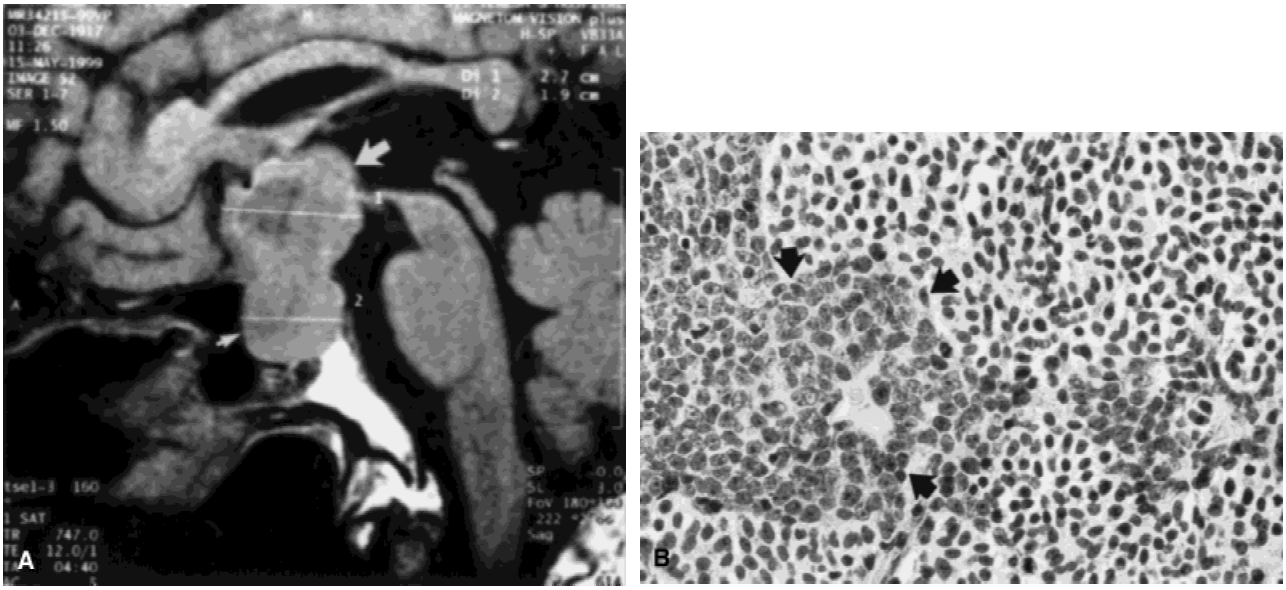

Fig. 1. (A) Turbo spin echo T1-weighted MRI sagittal scan of the pituitary fossa showed a bilobed tumor (arrow) arising from the pituitary, which bowed the pituitary fossa inferiorly and extended cranially to compress the optic chiasma and hypothalamus. A central hypointense hemorrhagic area is noted in the suprasellar component (large arrow). (B) Small sheets of large malignant lymphoid cells (arrows) intimately admixed with the pituitary adenoma cells. (Hematoxylin and eosin: magnification 250×.)

presented either as diabetes insipidus or were clinically silent [2,3]. Therefore, our case was unique in showing pituitary apoplexy with anterior hypopituitarism.

The unique localization to the pituitary gland and the intermingling between the lymphoma and adenoma cells is intriguing. Patients with pituitary adenomas were reported to have an increased risk of second malignancies, including lymphoma [4]. Furthermore, lymphoma cells possess endocrine hormone receptors, and growth of both T and B lymphoma cells can be stimulated by prolactin and other pituitary hormones [5]. A local concentration of pituitary hormones may favor the growth of lymphoma cells. On the other hand, the breaching of the blood brain barrier by the pituitary tumor may also allow easy access of the lymphoma cells to an immunologically privileged site for rapid proliferation.

In conclusion, we have shown that patients with anterior hypopituitarism caused by apoplexy, a metastatic lesion may be possible, of which lymphoma is one differential diagnosis, and careful exclusion of a primary neoplasm is warranted.

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Sarcoidosis Presenting as Massive Splenomegaly and Bicytopenia

To the Editor: Extrapulmonary sarcoidosis is unusual. Massive splenomegaly has been reported in only 3% of sarcoidosis patients [1]. We hereby describe an unusual case of sarcoidosis presenting as massive splenomegaly and bicytopenia.

A 53-year-old Yemenite Jewish female was referred to the hematology department for evaluation of splenomegaly and pancytopenia. Physical examination revealed a large and tense spleen palpable 15 cm below the left costal margin. The rest of the examination was otherwise unremarkable.

Her chest X ray was within normal limits; an ultrasonographic exam of the abdomen confirmed an enlarged spleen with a 20-cm span. White cell count was 2,100/μL with an absolute neutrophil count of 960 cells/μL. Hemoglobin was 13 g/dL, and the platelet count was 88,000/μL. Serum biochemistry was within normal limits. Bone marrow examination showed a hypercellular bone marrow with normal maturation of all cell lines.

The finding of an unexplained huge splenomegaly led us to suspect the possibility of splenic lymphoma and recommend splenectomy. A 1,600-g spleen was removed. Microscopic examination revealed multiple noncaseating granulomas with negative PAS and Ziehl Nielsen stains. An intraoperative liver biopsy revealed the same findings (Fig. 1a,b).

A diagnosis of sarcoidosis was made on the basis of these pathological findings.

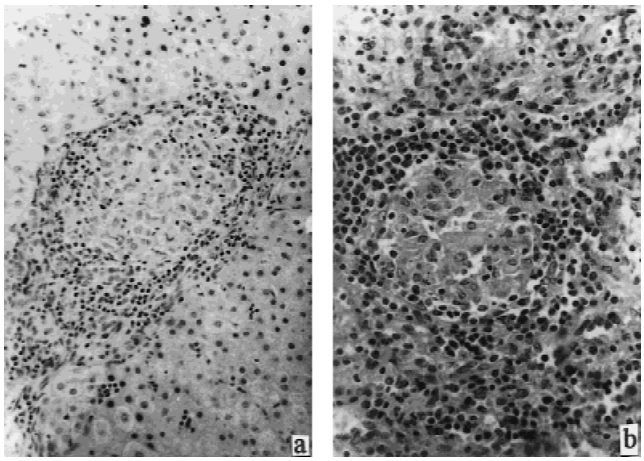

Fig. 1. Spleen (a) and liver (b) show multiple non-necrotizing epithelioid granulomas (H&E stain, ×150).

Post splenectomy, the patient had a complete resolution of her cytopenia. She required no further treatment. Repeat chest X rays and pulmonary function tests revealed no pathology. ACE (angiotensin converting enzyme) levels were up to 200 U/L on serial measurements (normal: 16–55).

Although extensive splenic involvement has been demonstrated in up to 63% of autopsy studies in sarcoidosis [2,3], massive splenomegaly occurring as a single clinical finding accompanied by different degrees of cytopenias has been reported in only a few cases. In most case reports the diagnosis of sarcoidosis was not entertained until after splenectomy [2]. The most common preoperative presumed diagnosis being lymphoma (as in our patient). Significantly elevated ACE levels in the face of a normal chest X ray (as in our patient) has also been seen in some of the cases.

We conclude that sarcoidosis should be considered in the differential diagnosis of a patient presenting with splenomegaly and cytopenia, even if there is no apparent involvement of any other organ system. Preoperative measurement of ACE levels, even though not diagnostic, may be a helpful lead.

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